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Immune Status in Newborns and Their Vulnerability

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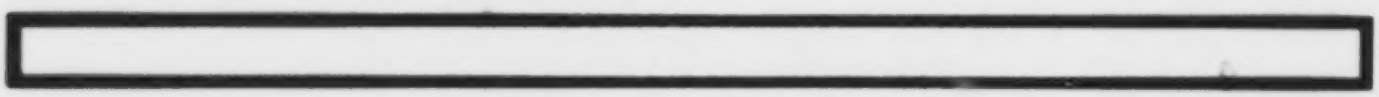

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IMMUNE STATUS IN NEWBORNS AND THEIR VULNERABILITY

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16. ABSTRACT

The most profound toxic effects of many physical and chemical agents are observed when exposure occurs during mammalian development. The development of immunocompetence in mammals involves a precise sequence of steps which begins during gestation and is completed during postnatal life. Perturbation or abrogation of this developmental sequenceof events may lead to life threatening dysfunctions as exemplified by certain heritable defects in immune system development. In light of this we have examined the effects that prenatal and/or early postnatal exposure to a variety of known or suspected physical and chemical immunomodulators may have on immune function in young adult rodents. Mice and/or rats were exposed in utero and/or during early postnatal life to the following agents: cyclophosphamide, nonionizing radiation, cyclosporin A, urethan, di-n-octyltin dichloride or $NiCl_2$. At immunological maturity (i.e., 6-8 weeks of age) animals exposed to these agents were assessed for immune system functional integrity. Immune function tests included the following: lymohoid organ and body weights, peripheral blood counts, lymphoproliferative responses to mitogens and allogeneic cells, natural killer cell activity, primary antibody responses to sheep erythrocytes, delayed hypersensitive responses, and resistance to tumor development. The results of these studies are summarized.

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Survival of mammalian species requires the presence of an intact functional immune system. The immune system is composed of myriad cellular and humoral components which are responsible for protecting the individual from invading microorganisms, eliminating foreign material, and destroying certain neoplastic cells. Evidence for the importance of a functional immune defense system comes from animal and human studies. For example, clinical studies indicate that the manipulation of the immune system in patients undergoing therapy for certain diseases or following organ transplant leads to an increased susceptibility to infectious agents and certain forms of neoplasia (1,2). Recently, the description of the disorder known as acquired immune deficiency syndrome (AIDS) has further underscored the critical role played by the immune system in survival (3). The lethality of this disorder is not due directly to the causative agent, but to squelae of compromised immunity. A majority of AIDS patients succumb to overwhelming infection with opportunistic microorganisms and may also develop rare forms of cancer. Over the years a growing body of evidence also indicates that a variety of natural and man made environmental agents are capable of modulating the immune system (4-7).

The development of the immune system in mammals involves a precise sequence of steps which begins early in gestation. Perturbation or abrogation of this developmental sequence of events can lead to immune dysfunctions which may be life threatening. Defects in the development of the immune system due to heritable changes in the lymphoid elements have provided clinical and experimental examples of the consequences of impaired immune development (8). For example, mice born with the

homozygous mutation (nu/nu) are hairless or "nude" and lack a thymus (9). These mice lack cell-mediated immune responses and are vulnerable to infection. Consequently, they do not generally survive more than a few weeks after birth unless raised in an environment that reduces exposure to pathogens.

The developing organism is in general more dramatically affected by exposure to physical or chemical agents than is the fully mature individual (10). For example, agents that normally require acute doses over a long period of time to produce cancer in adults may be capable of inducing cancer following dosing at a much lower level and over a shorter period of time during fetal development (11,12). Furthermore, the most profound effects of some agents that modulate the immune system occur when dosing of the compound begins during the development of the lymphoid system (5).

Potential functional defects caused by exposure to toxic agents during development range from life threatening suppression of vital components of the immune system to altered or poorly regulated responses that can be debilitating (13). The full extent of the immunological effects resulting from perinatal exposure to environmental agents is not yet known; however, the potential for serious consequences is obvious.

Over the past few years we have been investigating the effects that prenatal and/or early postnatal exposure to a variety of known or suspected physical and chemical immunomodulators may have on immune function in young adult rodents. Mice and/or rats have been exposed _in utero_ and/or during early postnatal life to the following agents: cyclophosphamide, nonionizing electromagnetic radiation, cyclosporin A,

urethan, di-n-octyltin dichloride, or nickel chloride. At immunological maturity (i.e., 6-8 weeks of age) animals exposed to these agents were assessed for immune system functional integrity. Immune function tests included the following: lymphoid organ and body weights, peripheral blood counts, lymphoproliferative responses to B and T cell mitogens and allogeneic cells, natural killer (NK) cell activity, primary antibody responses to sheep erythrocytes, delayed hypersensitivity responses and resistance to tumor development. The rsults of these studies are summarized in Table 1.

Based on the results of our work, it is difficult to categorically state that the developing immune system is more susceptible than the mature immune system to perturbation by the agents we have examined. We have found, that in the cases where we have studied it, immunosuppression in adult rodents is transient and reversible shortly following discontinuation of exposure to a given agent. This reversibility may explain why we have been unable to consistently observe alterations in immune parameters in animals treated perinatally and evaluated as young adults. However, it has been found that a prolonged (i.e., 4-6 weeks) suppression of mitogen responsiveness occurs following early postnatal exposure to di-n-octyltin dichloride. This suppression does not persist in adults treated with this chemical.

In light of the results obtained following early postnatal exposure of rats to di-n-octyltin dichloride, we plan to examine the effects of other agents administered during this period of immune development. Since immune development continues through the first four to six weeks of life in the rodent, it is not unreasonable to suspect that this period may be more sensitive to perturbation by certain drugs and chemicals.

Further research is needed to delineate the period during immune function development which is most susceptible to the action of drugs and chemicals. In addition, studies are warranted in which direct comparisons of altered immune function are made following drug or chemical exposure of functionally immature and mature rodents.

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REFERENCES

1. Cohen, J., A.J. Pinching, A.J. Rees and K.K. Peters (1982). Infection and immunosuppression. A study of the infective complications of 75 patients with immunologically-mediated disease. Quarterly J. Med., New Series Ll, No. 201:1.
2. Penn, I. (1981). Depressed immunity and the development of cancer. Clin. Exp. Immunol. 46:459.
3. Levine, A.S. (1982). The epidemic of acquired immune dysfunction in homosexual men and its sequelae-opportunistic infections, Kaposi's sarcoma, and other malifnancies: an update and interpretation. Cancer Treat. Rep. 66:1391.
4. Street, J.C. (1981). Pesticides and the immune system. In: CRC Immunmologic Considerations in Toxicology, Vol. I., Sharma, R.P. IEd.). CRC Press, Inc., Boca Raton, p. 45.
5. Vos, J.G. (1977). Immune suppression as related to toxicology. CRC Crit. Rev. Toxicol. 5:67.
6. Koller, L.D. (1979). Effects of environmental contaminanats on the immune system. Adv. Veter. Sci. Compar. Med. 23:267.
7. Koller, L.D. (1980). Immunotoxicology of heavy metals. Int. J. Immunopharmac. 2:269.
8. Heise, E.R. (1982). Diseases associated with immunosuppression. Environ. Health Perspectives 43:9.
9. Pantelouris, E.M. (1968). Absence of thymus in a mouse mutant. Nature (Lond.) 217:370.
10. Wilson, J.G. (1973). Environment and Birth Defects. Academic Press, New York, p. 1.

11. Miller, R.W. (1979). Perinatal carcinogenesis. J. Nat. Cancer Inst. Monogr. 51:3.

12. Drew, R.T., G.A. Boorman, J.K. Haseman, E.E.McConnell, W.M. Busey and J.A. Moore (1983). The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice, and hamsters. Toxicol. Appl. Pharmacol. 68:120.

13. Roberts, D.W. and J.R. Chapman (1981). Concepts essential to the assessment of toxicity to the developing immune system. In: Developmental Toxicology, Kimmel, C.A. and J. Buelke-Sam (Eds.), Raven Press, New York, p. 167.

14. Smialowicz, R.J., J.B. Kinn and J.A. Elder (1979). Perinatal exposure of rats to 2450-MHz CW microwave radiation: Effects on lymphocytes. Radio Science 14(65):147.

15. Smialowicz, R.J., C.M. Weil, J.B. Kinn and J.A. Elder (1982). Exposure of rats to 425-MHz(CW) microwave radiation: Effects on lymphycytes. J. Microwave Power 17:211.

16. Smialowicz, R.J., M.M. Riddle, R.R. Rogers and G.A. Stott (1982). Assessment of immune function development in mice irradiated in utero with 2450-MHz microwaves. J. Microwave Power 17:121.

17. Smialowicz, R.J., R.R. Rogers, R.J. Garner, M.M. Riddle, R.W. Luebke and D.G. Rowe (1983). Microwaves (2450 MHz) suppress murine natural killer cell activity. Bioelectromagnetics 4:371.

18. Luekbe, R.W., M.M. Riddle, R.R. Rogers, R.J. Garner, D.G. Rowe and R.J. Smilaowicz (1986). Immune function of young adult mice following in utero exposure to cyclophosphamide. J. Toxicol. Environ. Health 18:25.

19. Smialowicz, R.J., R.W. Luebke, R.R. Rogers, M.M. Riddle and D.G. Rowe (1985). Evaluation of immune function in mice exposed to Ordram®. Toxicology 37:307.

20. Smialowicz, R.J., R.W. Luebke, M.M. Riddle, R.R. Rogers and D.G. Rowe (1985). Evaluation of the immunotoxic potential of chlordecone with comparison to cyclophosphamide. J. Toxicol. Environ. Health 15:561.

21. Luebke, R.W., M.M. Riddle, R.R. Rogers, D.G. Rowe, R.J. Garner and R.J. Smialowicz (1986). Immune function in adult C57BL/6J mice following exposure to urethane pre- or postnatally. J. Immunopharmacology 8:243.

22. Luebke, R.W., R.R. Rogers, M.M. Riddle, D. G. Rowe and R.J. Smialowicz (1986). Alterations of immune function in mice following carcinogen exposure. Immunopharmacology (in press).

23. Smialowicz, R.J., R.R. Rogers, M.M. Riddle, D.G. Rowe and R.W. Luebke (1986). Immunological sdtudies in mice following in utero exposure to $NiCl_2$. Toxicology 38:293.

24. Smialowicz, R.J., R.R. Rogers, M.M. Riddle and G.A. Stott (1984). Immunologic effects of nickel. I. Suppression of cellular and humoral immunity. Environmental Research 33:413.

Table 1. The Effects of Agents on the Developing Immune System

Agent	Species	Dosing	Immune Effects	Reference
Nonionizing electromagnetic radiation	Rat	Prenatal	↑ mitogen response	(14,15)
	Mouse	Prenatal	↓ NK activity	(16)
	Mouse	Adult	↓ NK activity	(17)
Cyclophosphamide	Mouse	Prenatal	No consistent effects	(18)
	Mouse	Adult	↓ thymus, ↓ mitogen response ↓ delayed hypersensitivity and antibody response	(19)
	Rat	Adult	↓ thymus, ↓ mitogen response ↓ NK activity	(20)
Urethan (ethyl carbamate)	Mouse	Prenatal	↓ body wt., ↓ antibody response	
		Early postnatal	↓ NK and antibody response	(21)
		Adult	↓ spleen & thymus, ↓ mitogen response	(22)
Nickel Chloride	Mouse	Prenatal	↓ NK activity	(23)
		Adult	↓ thymus, NK activity, antibody response, ↑ tumors	(24)
Cyclosporin A	Mouse	Prenatal	No consistent effects	(Unpublished results)
		Postnatal (via milk)	↓ body weight	
Di-n-octyltin dichloride	Rat	Prenatal	No consistent effects	(Unpublished results)
		Postnatal (via milk)	No consistent effects	
		Early postnatal	↓ thymus, mitogen response	